71. A conjugate, comprising a polymeric carrier having a maximum of 100 monomeric units which contain 1-10 hapten molecules and 1-10 marker groups or solid phase binding groups which are coupled to identical reactive side groups at predetermined positions on the polymeric carrier, wherein the monomeric units are at least one member selected from the group consisting of nucleotides, nucleotide analogues, amino acids and peptide nucleic acids, and wherein the hapten molecules and the marker groups or solid phase binding groups are different from each other.

REMARKS

Claims 39-62 and 64-70 are currently pending. In this response, applicants amend claims 39-44, 49, 51, 55-60, 62, 64 and 66-67, and add new claim 71. Claims 39-62 and 64-71, as amended, are presented for reconsideration.

Applicants thank Examiner Ricigliano for the courtesy extended to applicants' representative in the personal interview of February 3, 1999. This response is directed to the topics discussed in the personal interview.

Claims 60 and 62 are rejected under 35 U.S.C. § 102(b) as being anticipated by Smith et al.

Claim 60 has been amended to indicate that the hapten molecules and the marker groups or solid phase binding groups are different from each other. This amendment distinguishes the invention from Smith. Different haptens and labelling groups are neither disclosed nor rendered obvious in view of Smith.

Claim 61 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Smith et al. in view of Buchardt et al.

As applicants noted above, claim 60 has been amended to avoid Smith. The addition of Buchardt would not overcome the failure of the primary reference Smith to show the invention. Therefore, applicants respectfully request that this rejection be withdrawn.

Claims 39-62 and 64-70 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner had four distinct objections to the claims, each of which will be discussed in turn.

First, the Examiner rejects the claims for reciting a peptide nucleic acid. The Examiner takes the position that this recitation is unclear, because the specification recites a peptide nucleic acid of a given formula (see page 7 of the specification), and also recites that the peptide nucleic acids are described in WO 92/20703. The Examiner takes the position that since the WO '703 reference shows far more embodiments than the recited formula, it is not possible to determine the metes and bounds of the invention.

As applicants noted in the personal interview, the specification clearly limits the peptide nucleic acids to those having the recited formula. It is noted that such peptide nucleic acids and their production are described in the WO '703 reference. Even though more embodiments than the formula recites are show in the WO '703 reference, applicants are merely referring to the reference for the production of compounds according to the recited formula.

The Examiner objected to the use of the term "hapten". The Examiner notes that in certain claims a "hapten" is defined as an immunologically reactive molecule. The Examiner takes the position that this definition appears to be contradictory to the accepted definition of a hapten, which is a molecule which cannot produce an immune response on its own, and hence cannot be immunologically reactive in accordance with the claims.

As applicants explained to the Examiner in the personal interview, the term "immunologically reactive molecule" in connection with the term "hapten" does not mean that the hapten sets off an immunological reaction in vivo, i.e., the production of antibodies. It means that the hapten is capable of binding to an already-present antibody in an in vitro diagnostic test.

Claim 56 is also objected to in reciting that the hapten can be a "metabolite" or "mediator".

As applicants noted in the personal interview, the term "metabolites" in accordance with the invention are defined in accordance with the ordinary meaning of the word as "substances reacted in biological metabolism". Those of skill in the art have a clear understanding of this term.

Regarding the term "mediator", the Examiner will note that this term has been deleted from claim 56.

Claims 60-60 (applicants assume the Examiner meant claims 60-62) and 64-65 are objected to because of the recitation that one of steps (a) and (b) is conducted.

As applicants noted in the personal interview, the claims clearly indicate that either or both of steps (a) and (b) may be conducted. Thus, the scope of the invention is not indefinite; rather, there are merely alternative ways in which the invention can be accomplished. This is not unclear, it is merely broad.

Claims 39, 41-51, 54-62 and 64-70 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Buchardt et al. (WO '703) in view of Bredehorst et al. Buchardt et al. is relied upon as teaching the synthesis and use of peptide nucleic acids. The PNAs are made of at least two monomers, preferably from 2 to 61 monomers (the Examiner

refers to page 7, line 10, which discloses that n is an integer from 1 to 60). Page 20, starting at line 26, is relied upon for the teaching that PNA molecules may be conjugated to reporter ligands (haptens are specifically mentioned on line 30). Moreover, Buchardt et al. is relied upon as teaching that the L groups (see Figure III on page 3), which is considered to read on groups coupled to reactive side chains, can be a fluorophore, radio or spin label or protein recognizing ligand such as biotin or a hapten (the Examiner refers to page 19, lines 5-8). The Examiner takes the position that since each L group is specifically located on the molecule in a location which is determined by the synthetic process under the control of the researcher, these groups are considered to be at "predetermined positions" on the polymer.

Pages 9-10 of the Office Action detail how Buchardt et al. is relied upon as teaching the limitations of several dependent claims.

The Examiner concedes that while Buchardt et al. teaches that multiple groups may be incorporated into or conjugated to a PNA molecule, the reference does not explicitly recite incorporating both marker groups and haptens or solid phase binding groups onto a single polymeric conjugate molecule. Bredehorst et al. is relied upon as making up for this discrepancy. Bredehorst et al. is relied upon as teaching the formation of carrier molecules formed from amino acids, with both hapten and multiple marker molecules placed at specific positions (the Examiner refers to Figure 1 of Bredehorst et al.). The Examiner takes the position that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate hapten and marker molecules as taught by Bredehorst et al. in a PNA molecule as taught by Buchardt et al, because Buchardt et al. teach the incorporation of haptens and markers into PNA

molecules at selected sites and Bredehorst et al. teach that it is known in the art to incorporate both a hapten and marker into the same conjugate.

This rejection is respectfully traversed.

Bredehorst uses a naturally occurring peptide, the insulin A-chain which contains a terminal amino group and three carboxyl groups distributed in a certain way along the protein chain. From this specific distribution of amino acids and sequence (terminal glycine and three glutamine acid residues) only a determined 3:1 stoichiometry of haptens and marker groups can be obtained. Other advantageous stoichiometries, e.g., in which a higher content of marker groups lead to a higher sensitivity, are not possible to obtain with this peptide. Moreover, the distance between the fluorescent groups is arbitrary, i.e., a very important optimization described in the present application for increasing the particularly critical fluorescence efficiency is not possible.

In Bredehorst there is no hint how a larger amount of marker groups could be introduced. It is disadvantageous that the three marker groups in Bredehorst can be incorporated only afterwards, which as is usually the case in organic reactions, implies corresponding yield losses since all marker groups must be introduced at the three positions simultaneously.

Buchardt describes oligomers of peptidic nucleic acids which can contain either marker groups or biotin. Contrary to the Examiner's point of view, Buchardt does not include any hint that different haptens or marker groups can be attached to an oligomeric carrier. Additionally, he does not hint on which measurements should be taken. In the present application new substances are described in which different molecules, (e.g. marker groups and haptens, biotins and haptens, etc.) can be attached at certain positions

of an oligomeric carrier at a desired, optional stoichiometric relation. These substances are very advantageous especially in immunoassays as is explained in example 4 of the present application.

Example 4 (which starts on page 26 of the specification) discloses the results of an experiment comparing conjugate I according to the invention (which is shown in Figure 3 and on page 26, line 4) and a reference conjugate (which is shown in Figure 4). As is clear from the description, conjugate I according to the invention contains two hapten molecules and two marker groups, while the reference conjugate only contains one hapten molecule and one marker group. It is clear from Table 2 (found on page 28 of the specification) that the conjugate according to the invention has a considerably improved test performance with regard to sensitivity and to lower detection limit compared to the reference conjugate. These advantages can be found when more than one hapten molecule and more than one marker group or solid phase binding group is used.

In order to stress these particular advantages of the invention, claim 39 has been amended to indicate that 2-10 hapten molecules and 2-10 marker groups or solid phase binding groups are located on the conjugate. Support for this change can be found in the paragraph bridging pages 7 and 8, and the first paragraph on page 9. Applicants refer the Examiner to the case In re Wertheim, 191 U.S.P.Q. 90 (CCPA 1976) with respect to changing numerical range limitations. See also MPEP Section 2163.05.

The Examiner will note that applicants have not amended the process claims (see claim 60) in this regard. Applicants submit that amending the process claims in this case is not necessary.

A remarkable feature of the present application is that when using identical monomeric units (e.g., lysine residues as components of the polymeric carrier) only the procedure according to the invention allows a concerted attachment of haptens and markers, which is neither disclosed in Buchardt or Bredehorst nor rendered obvious, respectively. This feature is now claimed in new product claim 71, and is already within the scope of the present method claims.

By the conventional labelling method, a statistical mixture of products (i.e., some of which have one or several of the desired haptens and/or marker or solid phase binding groups) is obtained. This product mixture contains the desire product, as well as a number of unwanted side products. Isolation of the desired product from the unwanted side products is essentially impossible. The method of the present invention, on the other hand, results in a uniform composition of conjugates having the desired properties, essentially without any unwanted side products. In order to highlight this advantage, applicants attach hereto a hand written explanation provided by the assignee.

An additional important feature of the invention is that only by applying the method according to the invention the stoichiometries (e.g., the number of the marker groups to the number of haptens) can be varied arbitrarily, determinedly, reproducibly and with a high yield. Such a concerted variation of the stoichiometries is not possible with any method described in previous publications. Whereas until now, those of skill in the art have depended on pure coincidence (statistic attachment), there now exists a technique which allows them to control both the positions and the stoichiometric relations of haptens and markers, with which they can carry out specified variations and generate reproducible optimized conjugates.

Upon review of claim 60, applicants noticed that this claim was too restrictive. The invention may be accomplished without cleavage of protective groups. Therefore, applicants have amended claim 60 to indicate the desired scope of the invention. Support can be found in the specification, as filed.

In view of the amendments and remarks above, applicants submit that this application is in condition for allowance and request reconsideration and favorable action thereon.

In the event this paper is not timely filed, applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 14-1060, along with any other fees which may be required with respect to this application.

Respectfully submitted,
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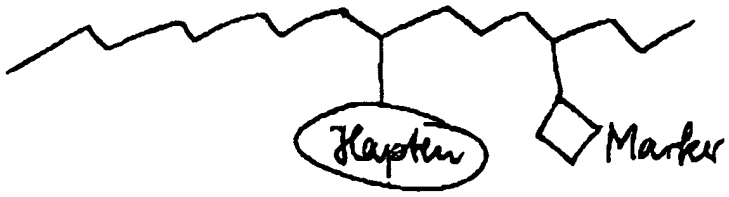
Attachments: Petition for Extension of Time

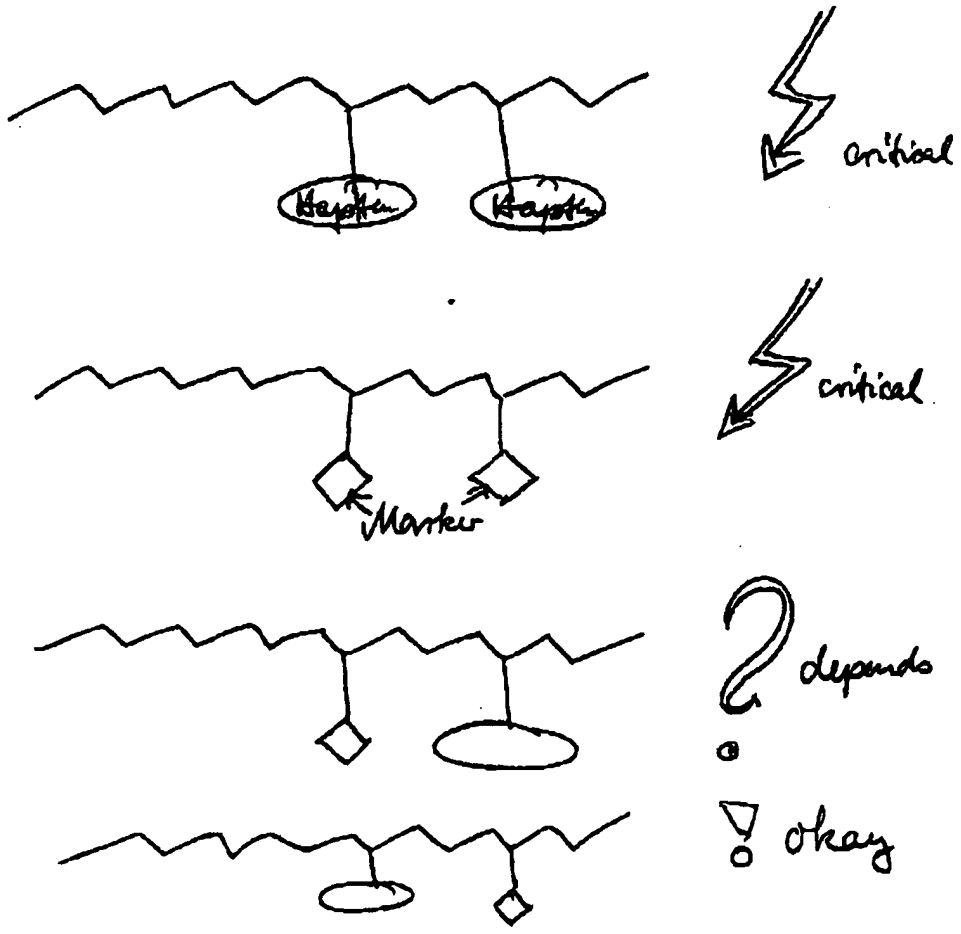
Only the invention can lead to a pre-determined and defined end-product (conjugate), when two or more <u>identical monomeric units</u> are (to be) used.

e.g.:



State-of-the-art-procedures will yield a statistical mixture; only part of the conjugates will be as desired other will not work or most likely interfere with the assay.

e.g.:



Abstract

The present invention concerns new conjugates, processes for their production as well as the use of these conjugates as antigens in immunological detection methods or for DNA diagnostics.